

What are good drug targets and how to find them?

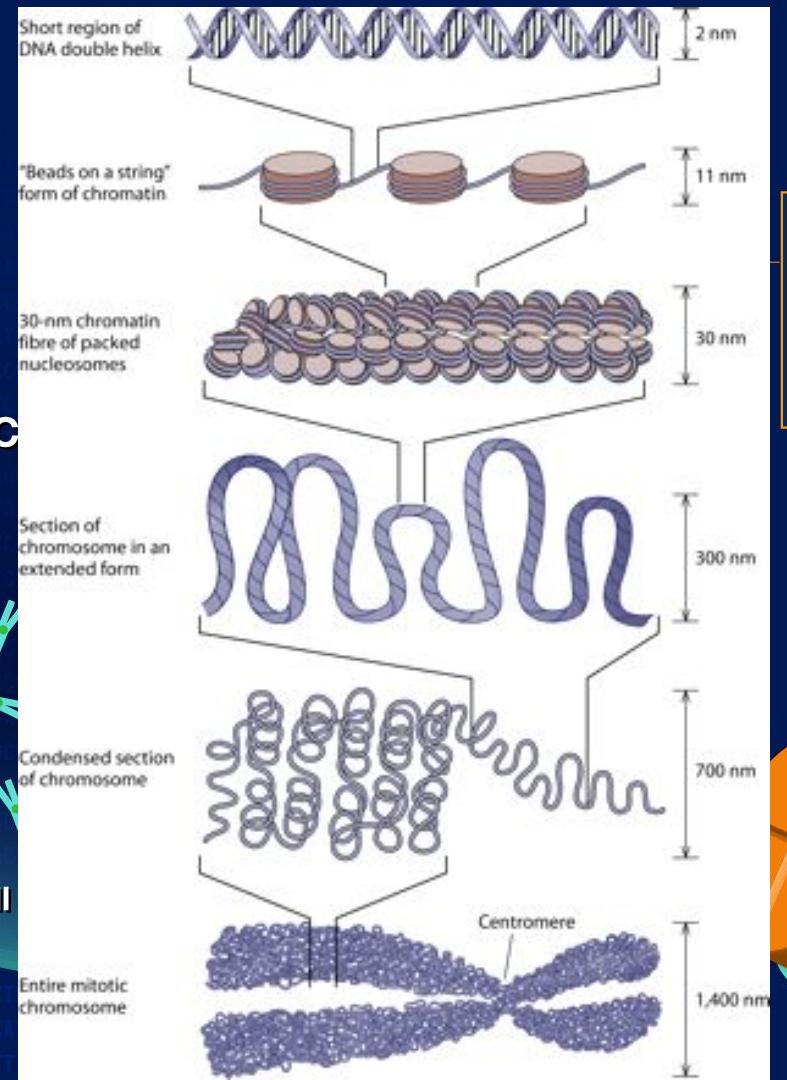
*Mathematical and Computational Biology in Drug
Discovery (MCBDD), Module I*

Dr. Jitao David Zhang, March 2022

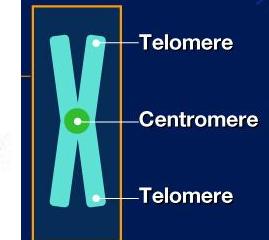
Outline

- We review biological foundations of target identification.
- Always write down numbers and possibilities for inference.
- Genetics doubles the success rate of target identification.

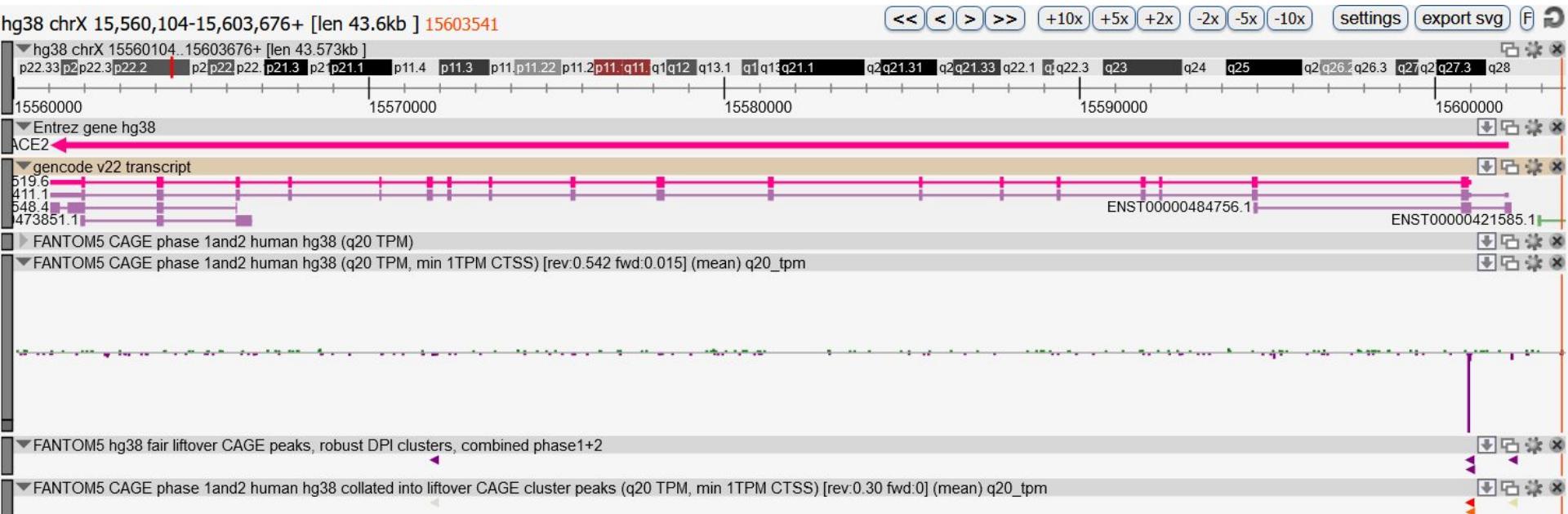
Chromosome



NHGRI FACT SHEETS
genome.gov



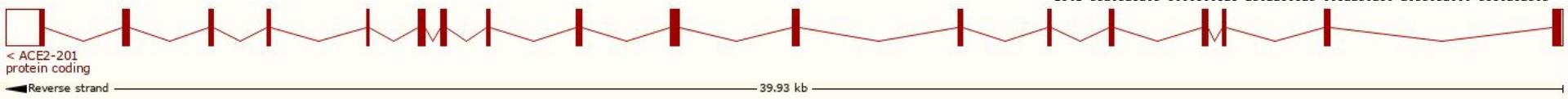
Gene structure and gene expression



ACE2 viewed in FANTOM5/ZENBU

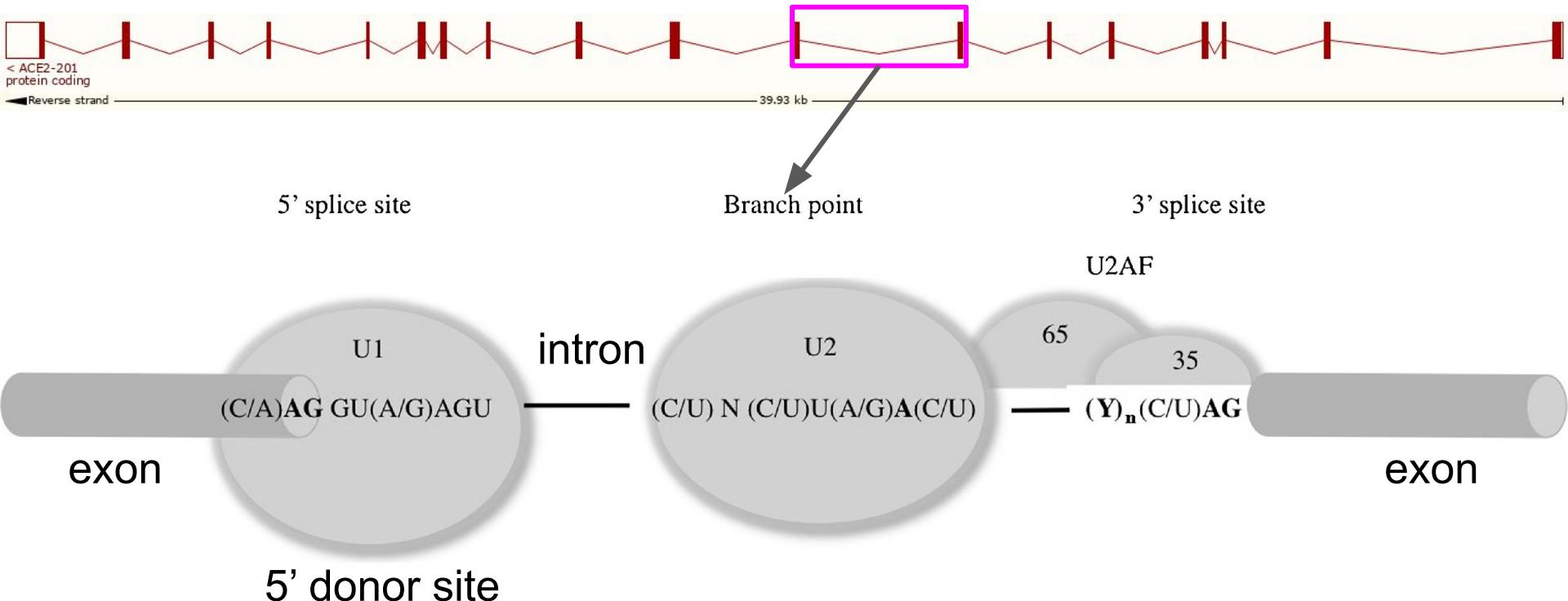
A mRNA of ACE2

- RefSeq record [NM_001371415.1](#)
- EnsEMBL record
[ENST00000252519.8](#)
- Red and blue boxes: start codon (ATG) and stop codon (TAG). The region between them is called the *coding sequence* (CDS).



1 agtcttaggaa aagtcatcca gtggatgtga tcttggctca caggggac **a** tg caagctc
61 61 ttccctggc tccttcgc ttgtgtgt aactgtgtc cagttccactt cttggggaaaca
121 121 ggccaaagaca ttttggacaa agttttaacc aacaaatata tactgaagaa atatgtccaa acatataaa
181 181 acttgcttc ttggattataa acacaaatata tactgaagaa atatgtccaa acatataaa
241 241 tgctggggac aaatgggtc cttttttttt 555 ggacatgc acatctggcc aaatgtatcc
301 301 ggtttttttt cttttttttt 555 gtttggacaa gtttggatgtc cttttttttt 555 cttttttttt 555
361 361 gttttttttt cttttttttt 555 acggggacaa acggggacaa acatctggcc acatataaa
421 421 cttttttttt 555 cttttttttt 555 acggggacaa acggggacaa acatataaa
481 481 tggggaaago ttggatgtc cttttttttt 555 cttttttttt 555 cttttttttt 555
541 541 tggggaaago ttggatgtc cttttttttt 555 cttttttttt 555 cttttttttt 555
601 601 ggtttttttt 555 cttttttttt 555 cttttttttt 555 cttttttttt 555 cttttttttt 555
661 661 agggactat gaatgtttttt 555 gggatgtatc ctatgtatc agcggcgcc agtttggatgt
721 721 agatgtgtggaa cttttttttt 555 aagatgtatc accatattttt 555 gaaatcttc
781 781 gggggcaagtttggatgtc cttttttttt 555 cttttttttt 555 cttttttttt 555
841 841 tttttttttt 555 gggatgtatc cttttttttt 555 gggatgtatc cttttttttt 555
901 901 tttttttttt 555 gggatgtatc cttttttttt 555 gggatgtatc cttttttttt 555
961 961 aacaaatata ttccaaagggg ccggggatgtt cttttttttt 555 cttttttttt 555
1021 1021 ttccaaagggg ccggggatgtt cttttttttt 555 cttttttttt 555 cttttttttt 555
1081 1081 ccatccccca gctttttttt 555 gggggggcc ttgggggggg cggctttttt 555
1141 1141 gaaatgtatc cttttttttt 555 cttttttttt 555 cttttttttt 555
1201 1201 atatgtgtca cttttttttt 555 ttggatgtatc cttttttttt 555
1261 1261 tggggaaatcc atgtttttt 555 ctggatgtatc cttttttttt 555
1321 1321 gtcacccggat ttccaaaggaa aacaaatata ttccctgtcc aacaaatata
1381 1381 cacgattttt 555 gggactcttc cttttttttt 555 cttttttttt 555
1441 1441 taaaggggaa atttttttt 555 accatgtatc gaaaatgtatc tttttttttt 555
1501 1501 agttttttttt 555 ttggggaaatcc tttttttttt 555 cttttttttt 555
1561 1561 coaatgtttt aatgtttttt cttttttttt 555 cttttttttt 555
1621 1621 gtttcaagaa gcaatttttt 555 aagatgtatc acatgtatc cttttttttt 555
1681 1681 ttccaaatcc atcaatgtatc gacaaatgtatc gtttcaatcc cttttttttt 555
1741 1741 acctttggccatcc ttccatgtatc cttttttttt 555
1801 1801 gtttcaatcc ttccatgtatc cttttttttt 555
1861 1861 gggatgtatc accatgtatc gtttcaatcc cttttttttt 555
1921 1921 aatcatgtatc cttttttttt 555 aacaaatata atccaaatata
1981 1981 atccatgtatc cttttttttt 555
2041 2041 tttttttttt 555 gggatgtatc gtttcaatcc cttttttttt 555
2101 2101 tttttttttt 555 gggatgtatc gtttcaatcc cttttttttt 555
2161 2161 cttttttttt 555
2221 2221 tttttttttt 555
2281 2281 tttttttttt 555
2341 2341 gtttcaatcc cttttttttt 555
2401 2401 cttttttttt 555
2461 2461 cttttttttt 555
2521 2521 tttttttttt 555
2581 2581 tttttttttt 555
2641 2641 tttttttttt 555
2701 2701 tttttttttt 555
2761 2761 tttttttttt 555
2821 2821 tttttttttt 555
2881 2881 tttttttttt 555
2941 2941 tttttttttt 555

The splicing code



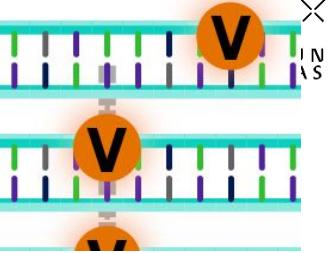
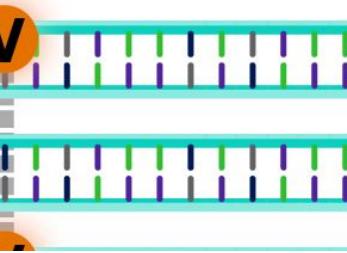
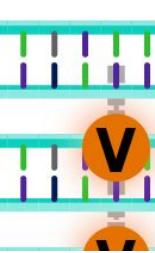
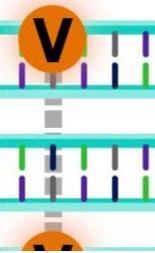
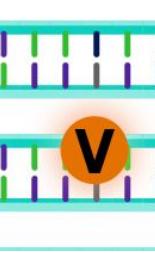
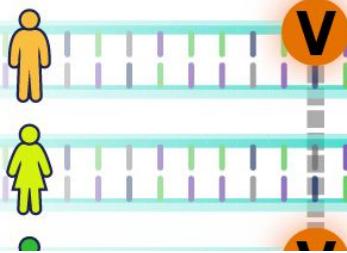


Person one

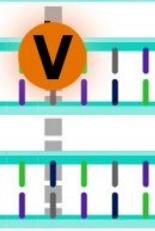
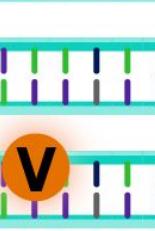
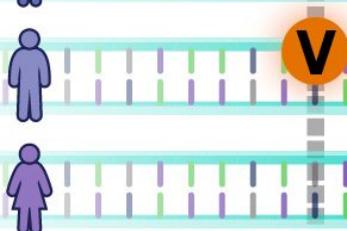
A G A C G C T

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
17-7579017-C-T	E	c.74+22G>A	● intron		Likely benign		1
17-7579831-C-T	E	c.74+8G>A	● splice region		Likely benign		1
17-7579924-G-A	E G	c.-12C>T	● 5' UTR		Likely benign		7
17-7579932-G-C	E	c.-20C>G	● 5' UTR		Likely benign		2
17-7578142-C-A	E G	c.672+35G>T	● intron		not provided		9
17-7577142-C-A	E	p.Gly266Ter	● stop gained		Pathogenic		1
17-7578188-C-A	E	p.Glu221Ter	● stop gained		Pathogenic		1
17-7578263-G-A	E	p.Arg196Ter	● stop gained		Pathogenic		1
17-7576928-TAGGAA...	E	c.920-14_920-3delTGC...	● splice region		Uncertain significance		2
17-7578171-C-A	E G	c.672+6G>T	● splice region		Uncertain significance		2
17-7578171-C-T	E	c.672+6G>A	● splice region		Uncertain significance		1
17-7579934-C-T	G	c.-22G>A	● 5' UTR		Uncertain significance		1
17-7565206-T-A	G	c.*51A>T †	● 3' UTR				1
17-7565222-C-T	G	c.*35G>A †	● 3' UTR				1

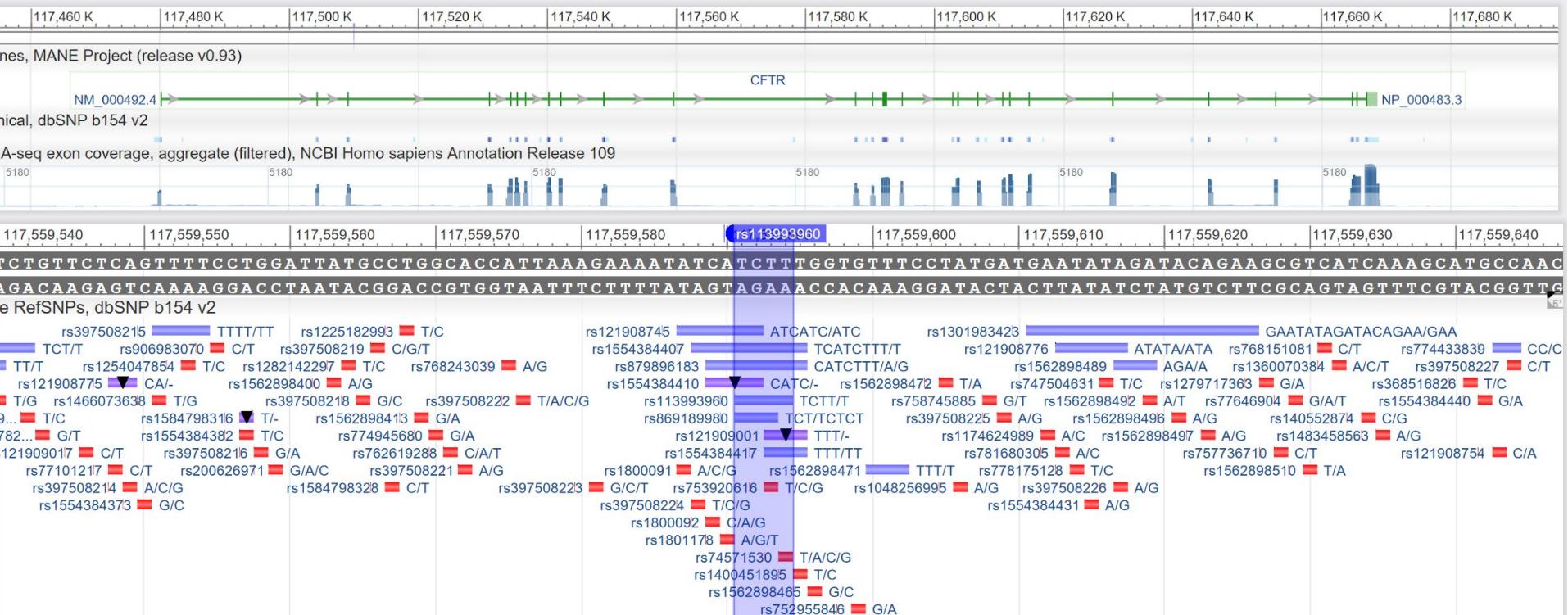



a

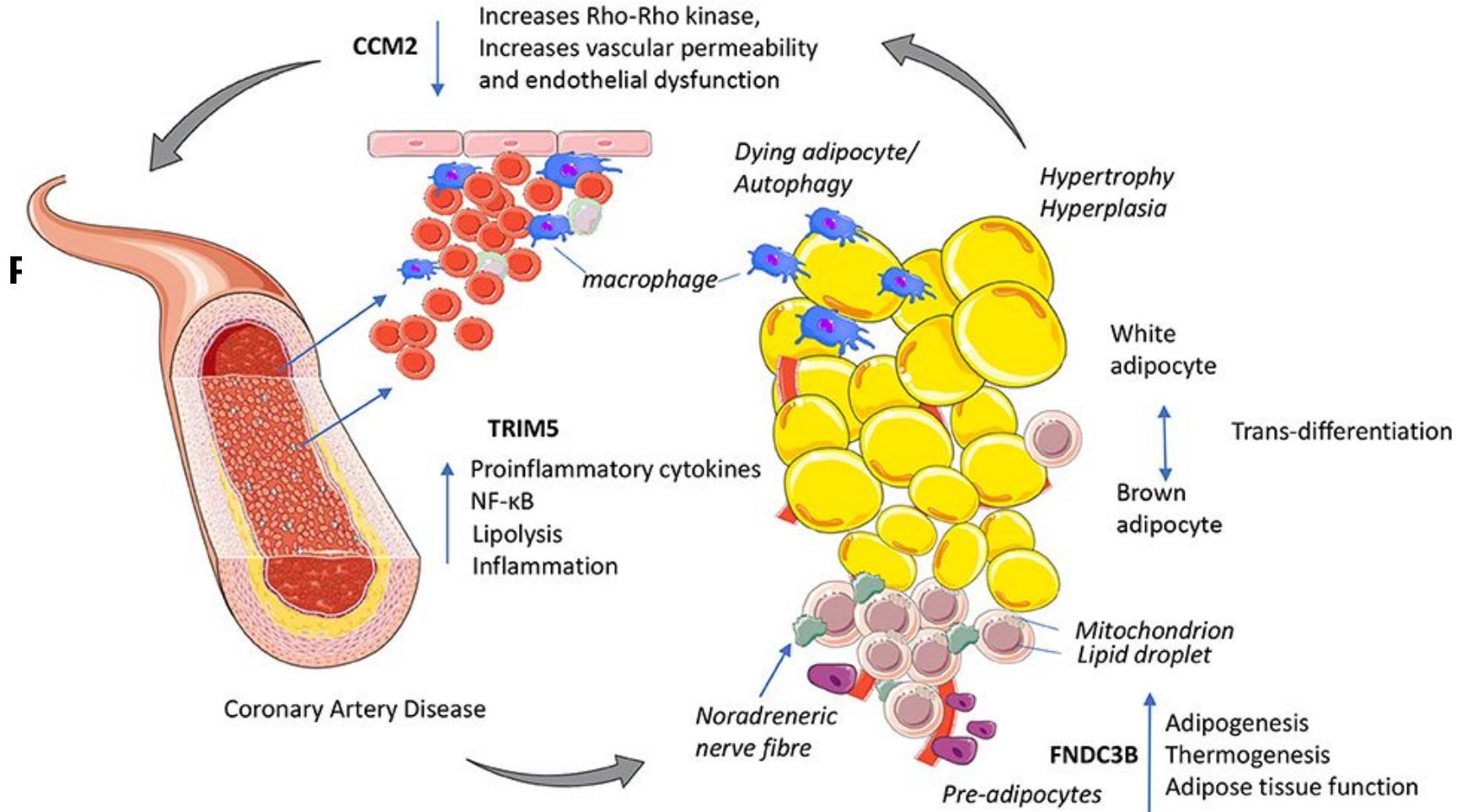
SV class	CNV			Other SV (non-CNV)				Unresolved
	Deletion	Duplication	Multiallelic CNV	Insertion	Inversion	Translocation	Complex SV	Breakends
Abbrev.	-DEL	-DUP	-MCNV	-INS	-INV	-CTX	-CPX	-BND
Ref.								
Example alternatives								
							(See Fig. 2)	Discarded



Cystic fibrosis

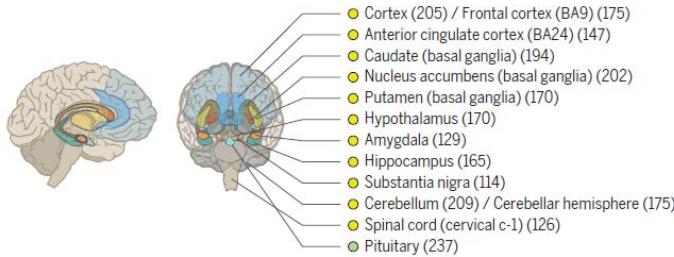


The *CFTR* gene (Chr 7), and rs113993960, the most common cause of CF



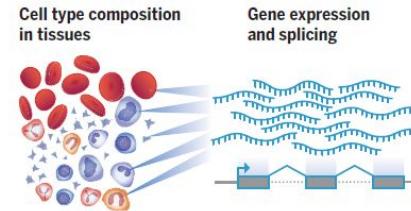
Dna Se

A



B

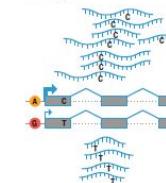
Cell type composition
in tissues



Gene expression
and splicing

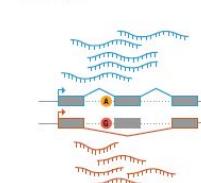
Expression quantitative
trait loci (eQTLs)

cis-eQTLs

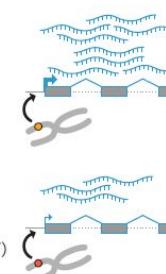


Splicing quantitative
trait loci (sQTLs)

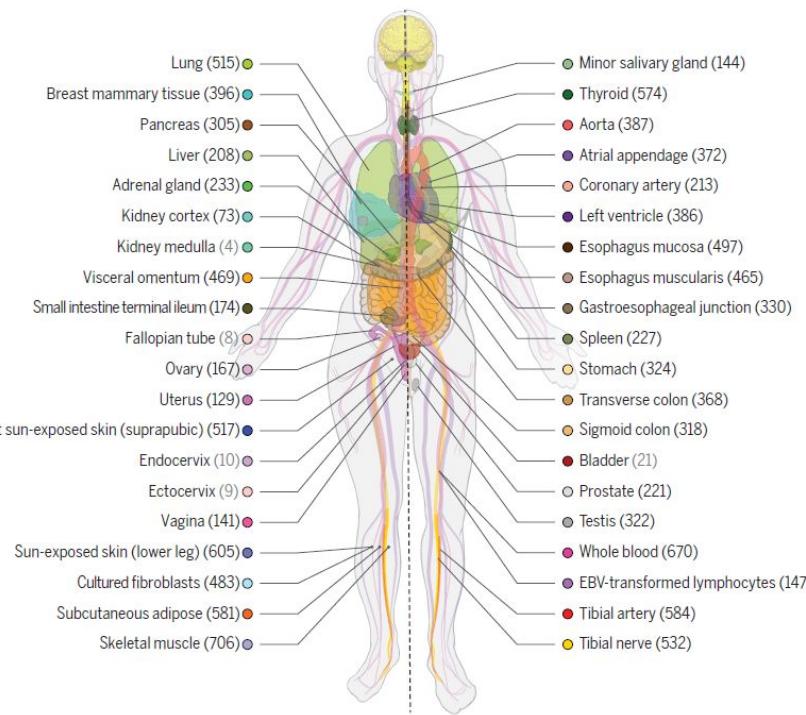
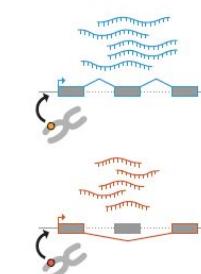
cis-sQTLs



trans-eQTLs



trans-sQTLs



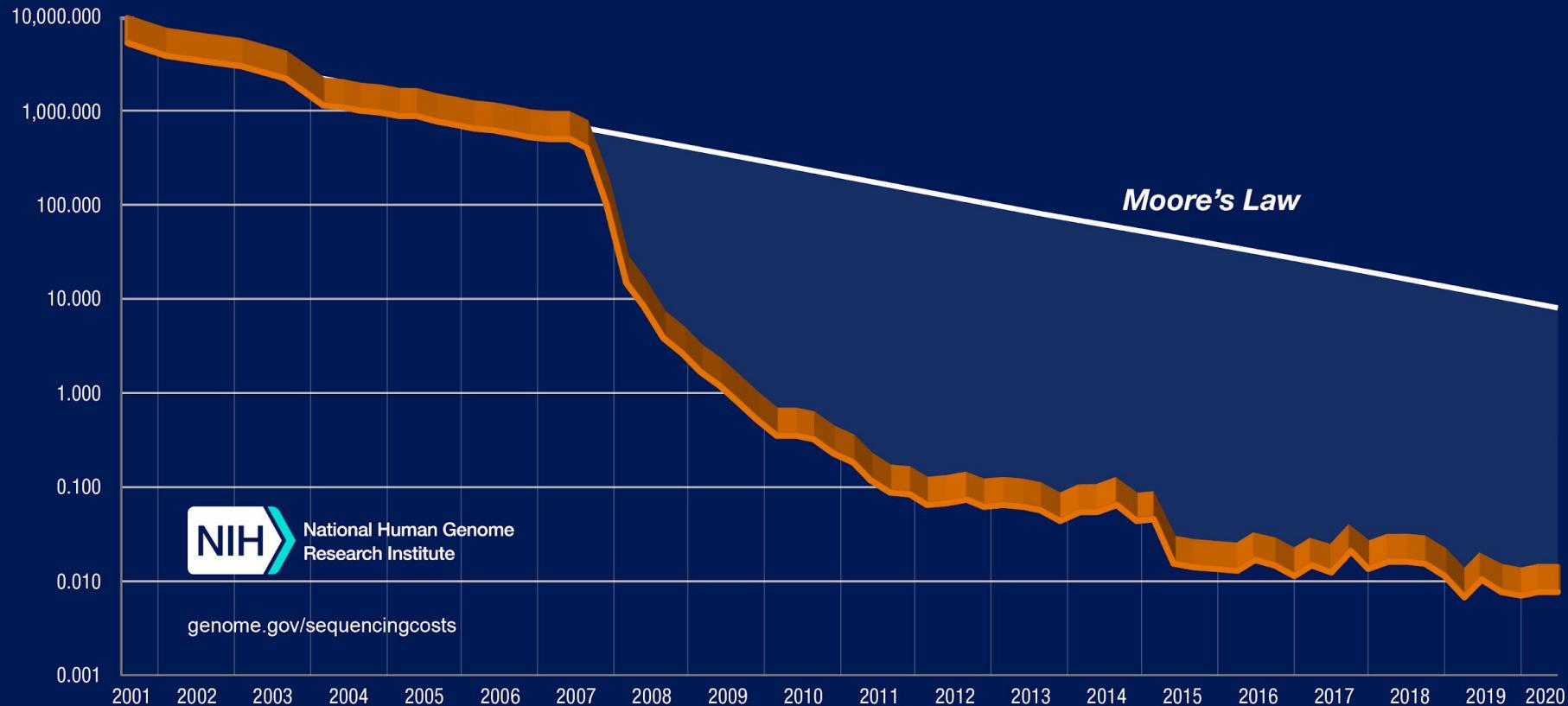
FACT SHEETS
genome.gov

GTEX (v8)



National Human Genome
Research Institute

Cost per Raw Megabase of DNA Sequence



National Human Genome
Research Institute

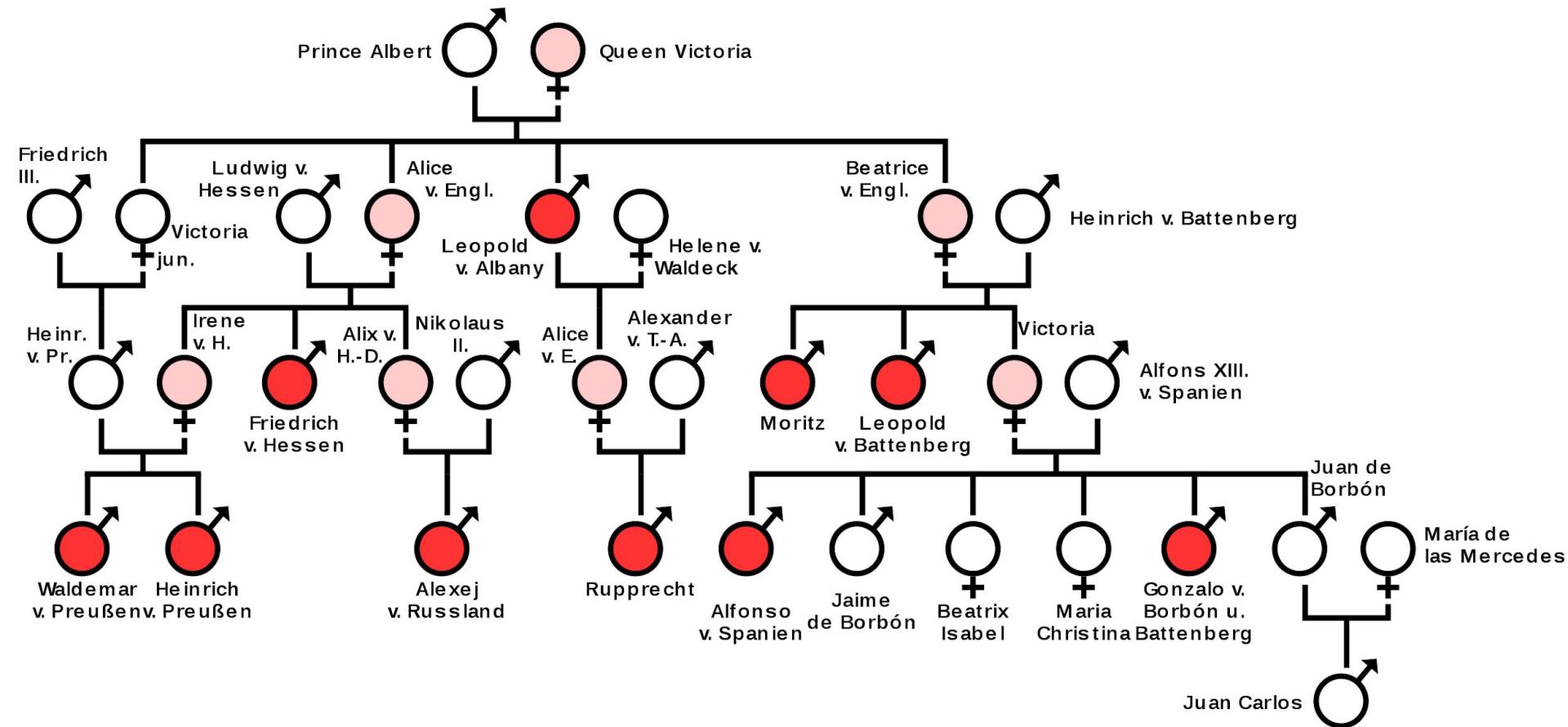
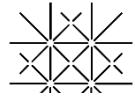
genome.gov/sequencingcosts

Cost per Human Genome



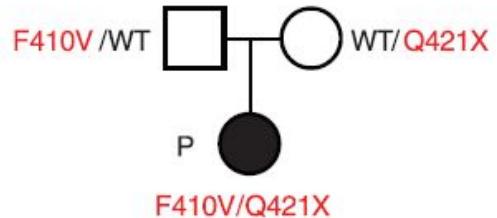


Haemophilia in the descendants of Queen Victoria

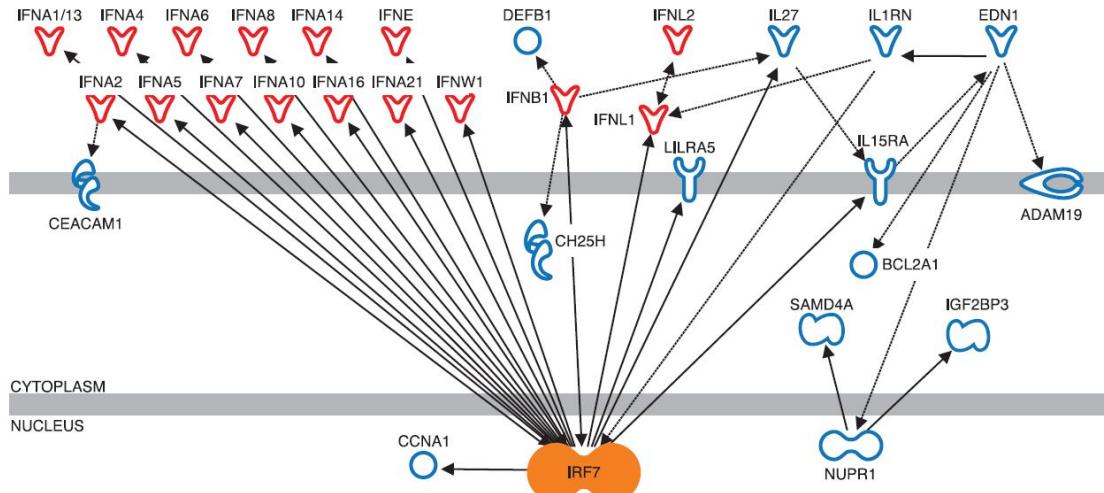
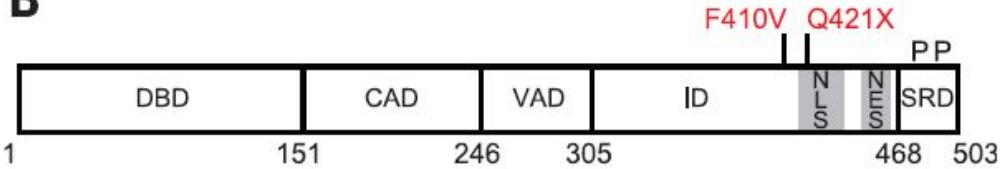


Life-threatening influenza infection in human IRF7 deficiency detected by trio sequencing

A



B



Exercise of *inference* (I)

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2, which is pending regulatory agency's review. The test has been shown to have a sensitivity of 99% and a specificity of 99%.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. Assume that 5% of the population is in fact infected. Was is your guess about the probability that Fred is indeed infected?

(Sensitivity is predicted true positive divided by all true positive; specificity is predicted true negative divided by all true negative).

Exercise of *inference* (I) - variants

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2 which is pending regulatory agency's review. When test with 100 SARS-Cov-2 patients, 99 report positive and one reports negative. When test with 100 healthy volunteers, 99 report negative and one reports positive.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. There are 30,000 people in the city where Fred lives; among them 1,500 are infected with SARS-Cov-2. What is the likelihood that Fred is truly infected given his positive test?

Exercise of *inference* (II)

I have three pills and two hamsters. The two hamsters look identical, while one carries a genetic mutation that affects its response to the pills.

1. Pill A makes both hamsters sleep.
2. Pill B makes neither animal sleep.
3. Pill C makes one animal sleep but not the other.

Now I pick a pill, feed it to one hamster, and the hamster falls asleep. What's the probability that the pill makes the other animal sleep, too?

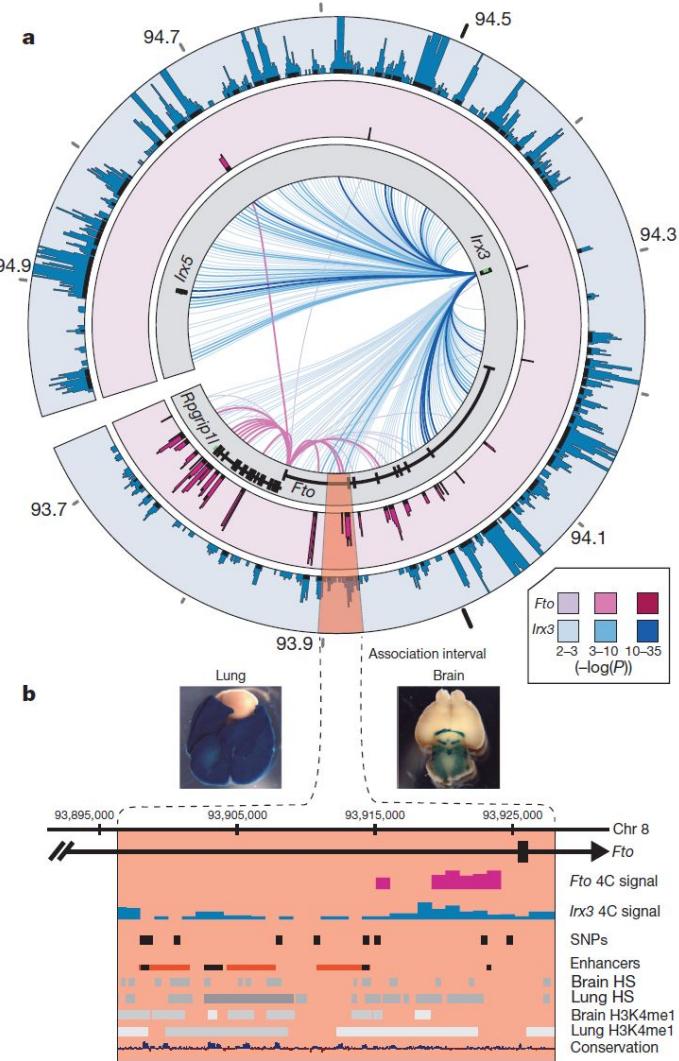
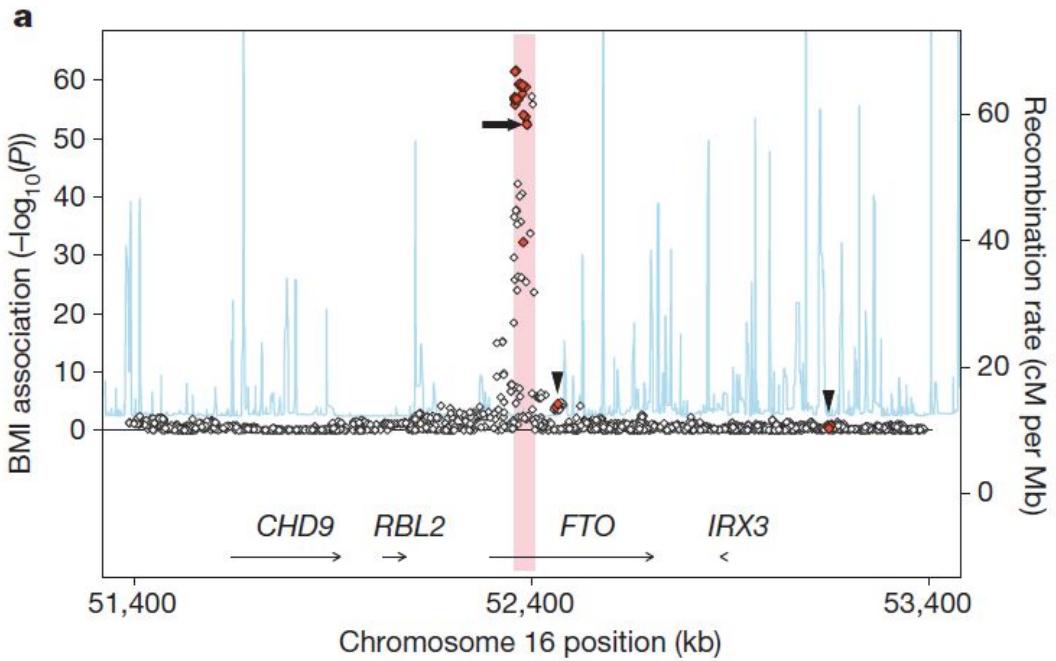
Exercise of *inference* (III)

- Cao and Moult (BMC Genomics, 2014) reported studied overlap between drug targets and GWAS hits.
- Use the data in the Table 1 of the paper ([cloned here](#)) to answer following the following two questions:
 - a. Assuming we know *nothing* about a gene (let's call it gene *WKN1*), what is the probability that the gene is a target for a disease listed here?
 - b. Assuming that we know nothing about another gene *WKN2* but that it is a GWAS hit for a disease, what is the probability that *WKN2* is a target for that disease?

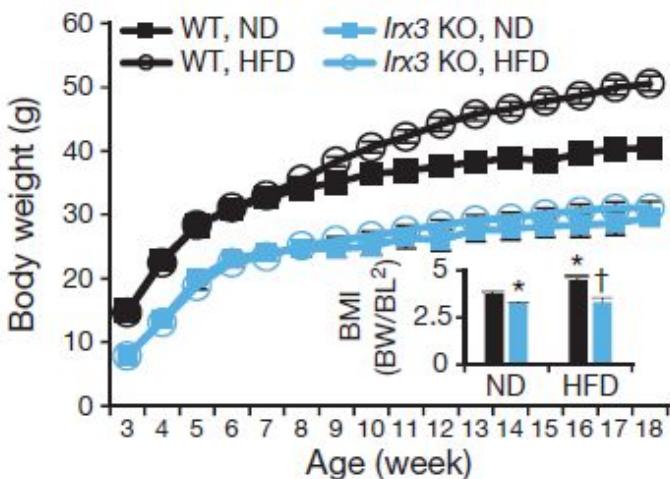
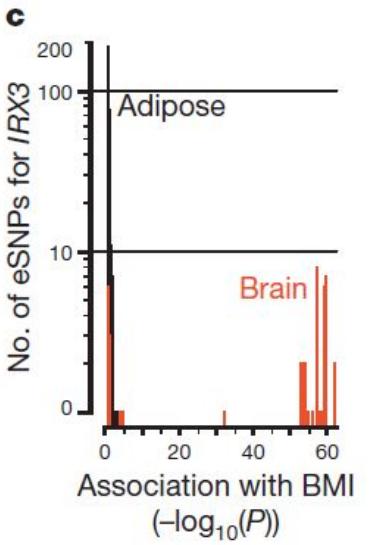
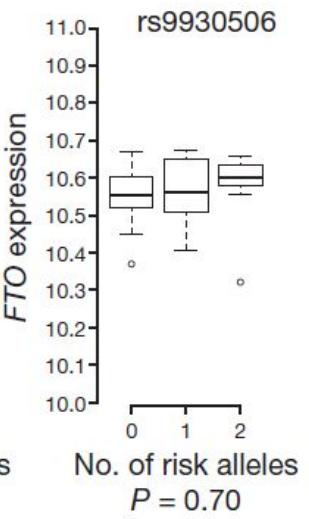
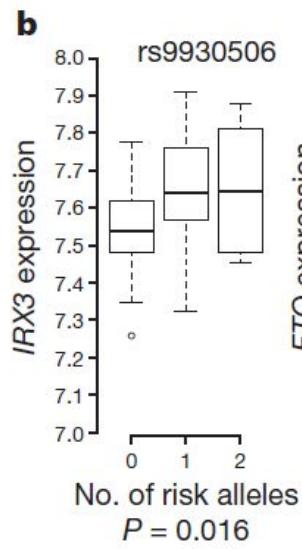
Offline activities of Module I

Due on March 31st, <https://forms.gle/KQm4GQxxBq1odVgE9>

Is FTO a good target for obesity?



If at all, **IRX3** is a more probable target



Recap of the biology we talked about last time



ACE2 viewed in **NCBI Genome Browser**

The Human
Genome
and
Variations

Gene
Structure
and gene
expression

DNA and
RNA
sequencing

Recap of the math we talked about last time

- **Always write down your probabilities.**
- The probability theory and the Bayes theorem for inference.

	Sensitivity	Specificity
NPS	86% (90% CI 77–93)	99.93% (90% CI 99.77–99.99)
Saliva	92% (90% CI 83–97)	99.96% (90%CI 99.85–100)

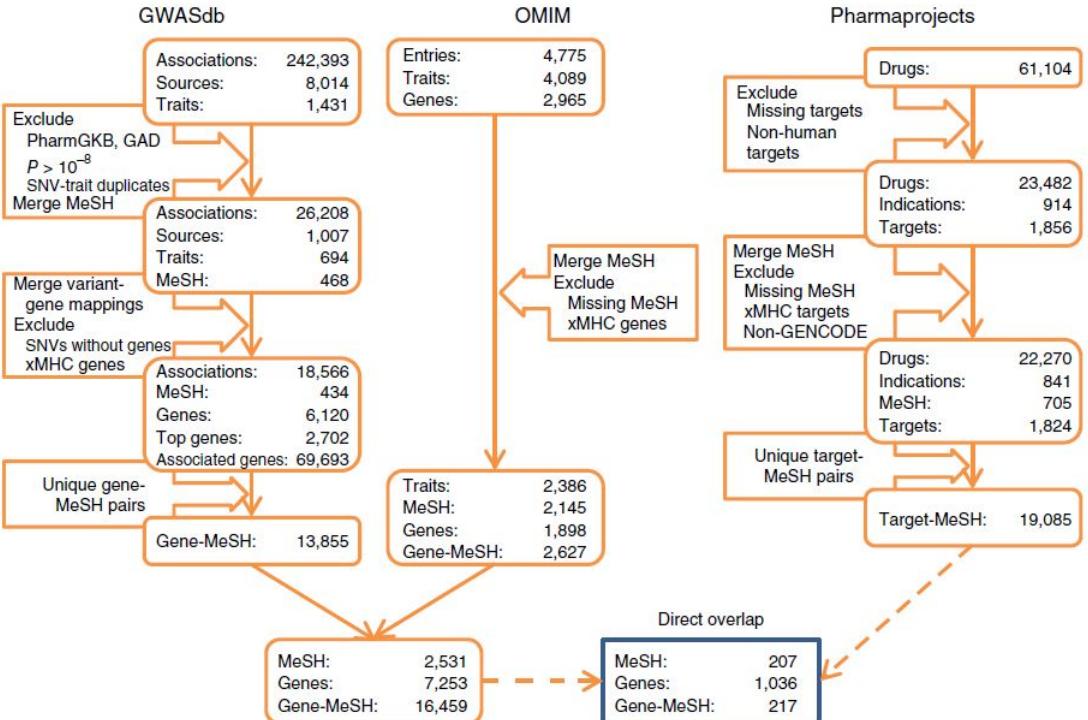
NPS = nasopharyngeal swabs. [Yokota et al., 2020](#)

- A list of approved serological tests and their accuracy can be found [here](#);
- Does He Have It? by Bill Casselman (AMS)

Other questions

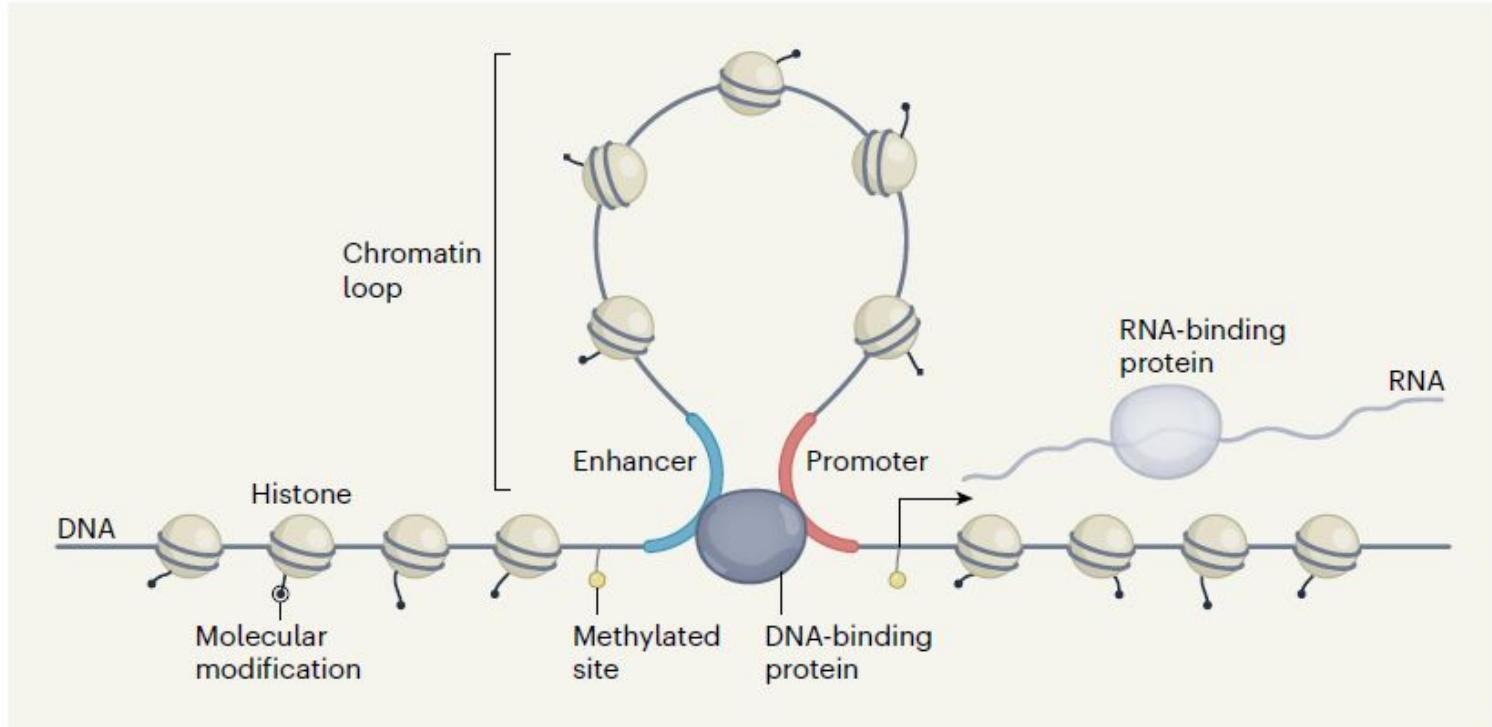
- Why I recommended the GOT-IT paper? How can academia and industry work together towards good targets?
- Did sequencing cost always follow the Moore's law?
- What happens if there are ATGs (AUGs in RNA) in 5'-untranslated region?
 - In some cases, there are alternative start codons;
 - However, in most cases, the ATGs in 5'-untranslated region seem to be always ignored by the translational machinery. A study (Rogozin, Bioinformatics, 2001) suggested that those AUGs may ensure low basal expression and generate regulatory elements.
- Which target level (gene or protein) is more useful for the target identification?
In the lecture, gene-level approach seems not so promising.
- Is blue eyeness a marker of Neanderthalian origin? *The story of OAC2*

Impact by a factor of ~2 estimated by Nelson et al.

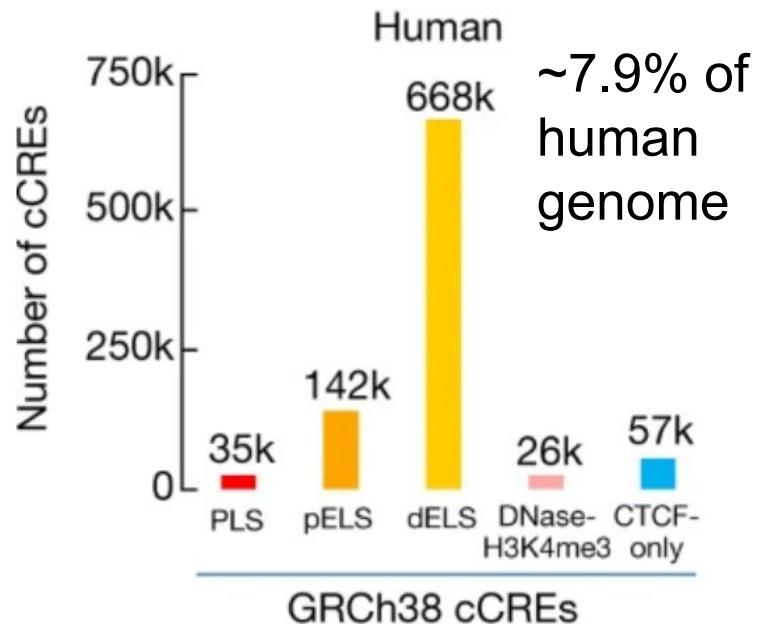
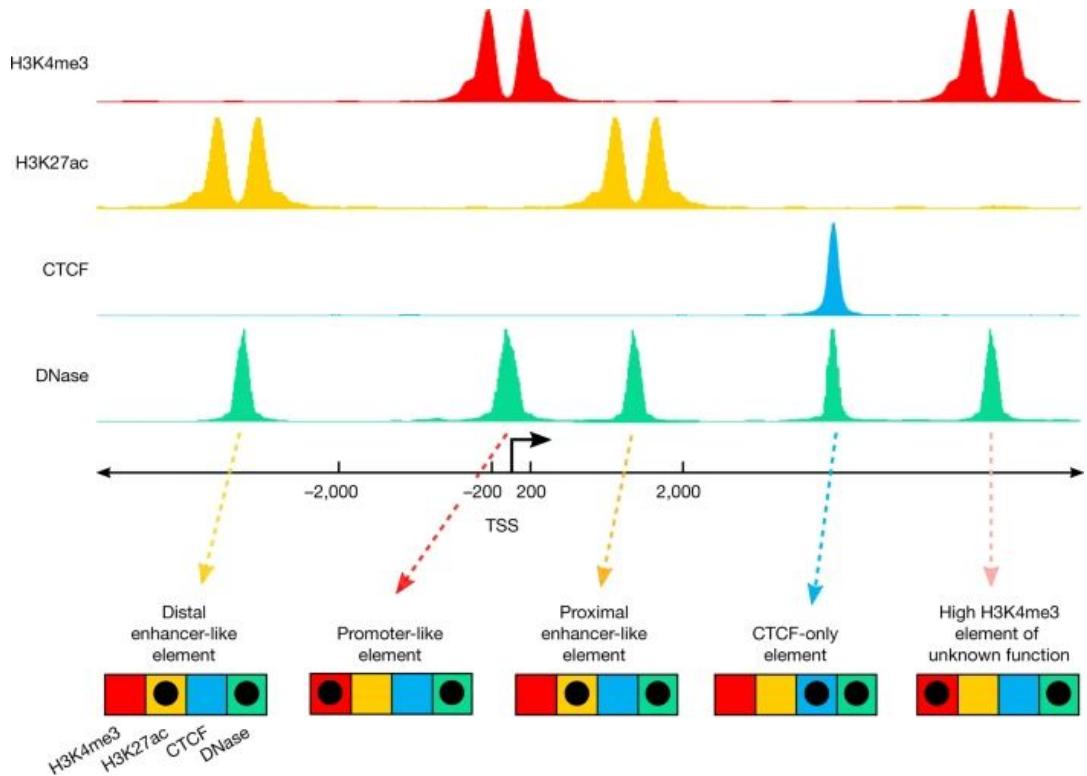


Disease \longleftrightarrow Gene \longleftrightarrow Drug

Much of the non-coding genome is junk, some is regulatory



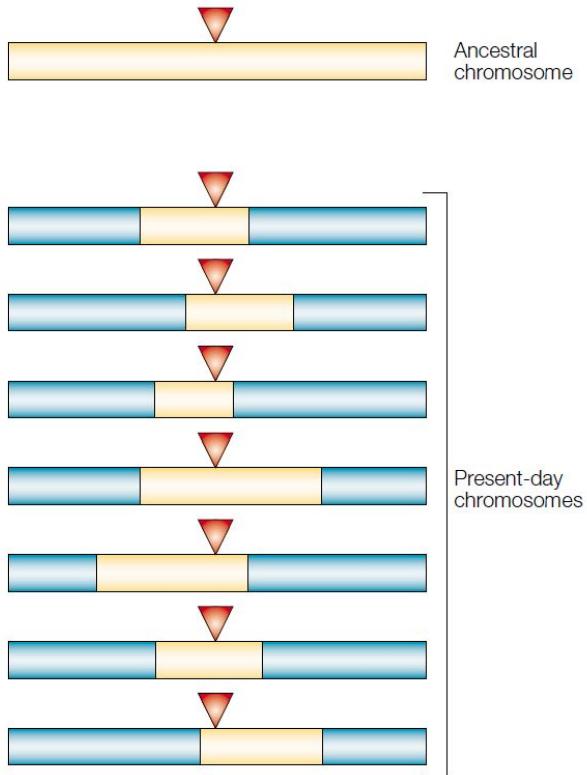
Candidate cis-regulatory elements (cCRE)



<https://screen.encodeproject.org/>

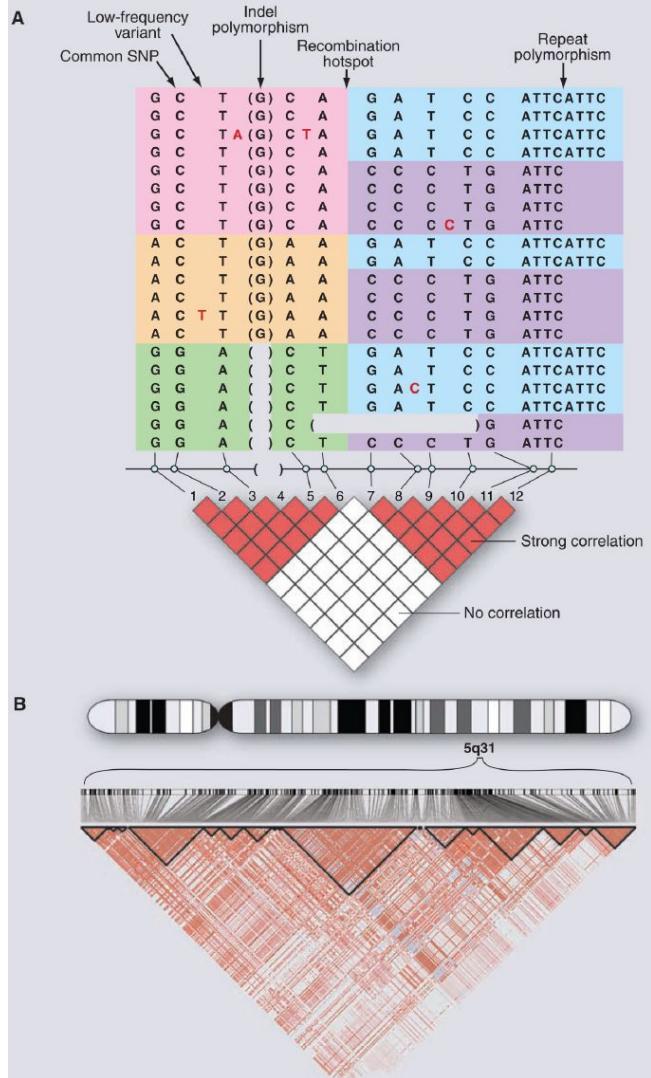
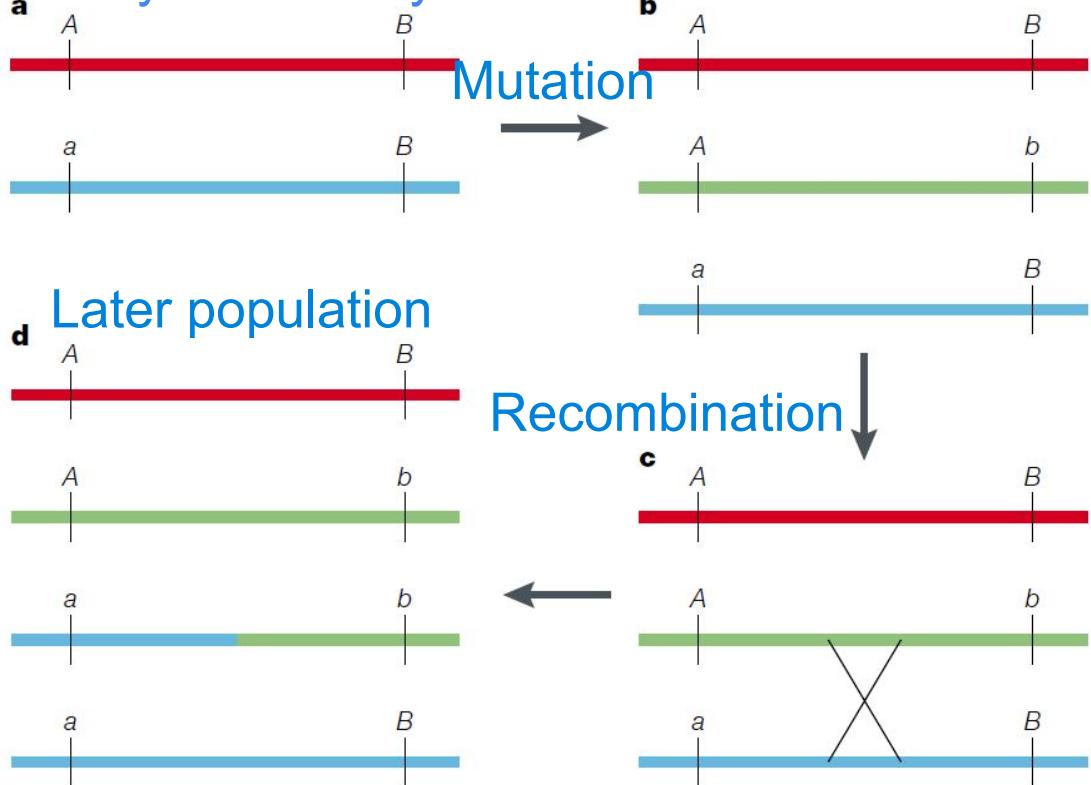
Linkage Disequilibrium in human genome

Particular alleles (single gene copies) at neighbouring loci tend to be co-inherited. For tightly linked loci, this might lead to associations between alleles in the population. This property is known as linkage disequilibrium (LD).

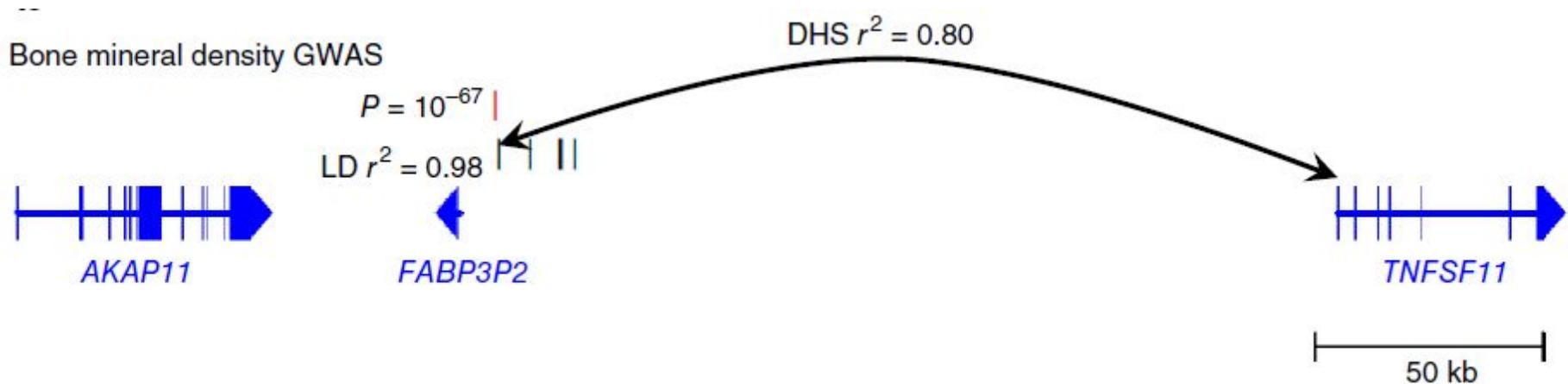


Population genetics helps with disease mapping

Early in ancestry



Correlation between DNase I hypersensitive (DHS) sites helps linking genetic variants with genes



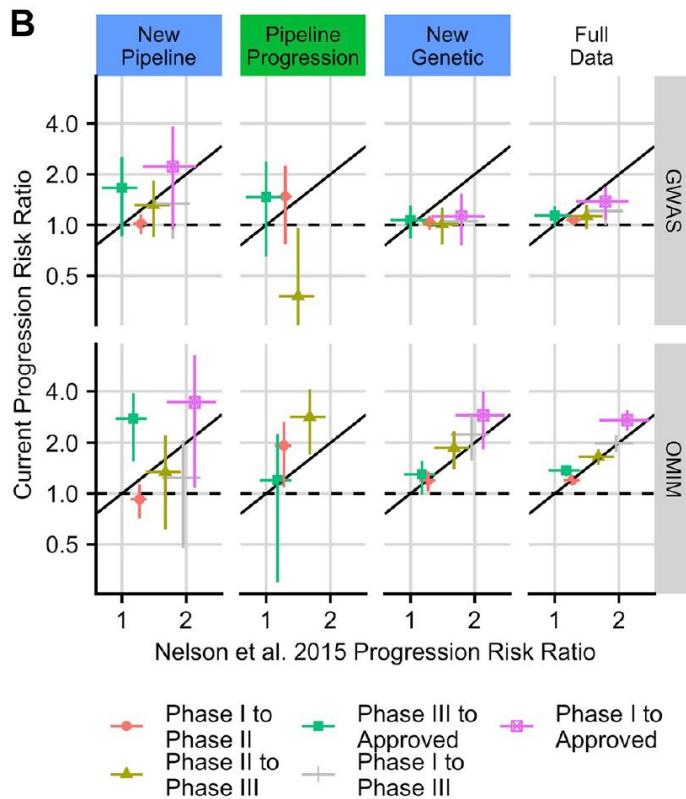
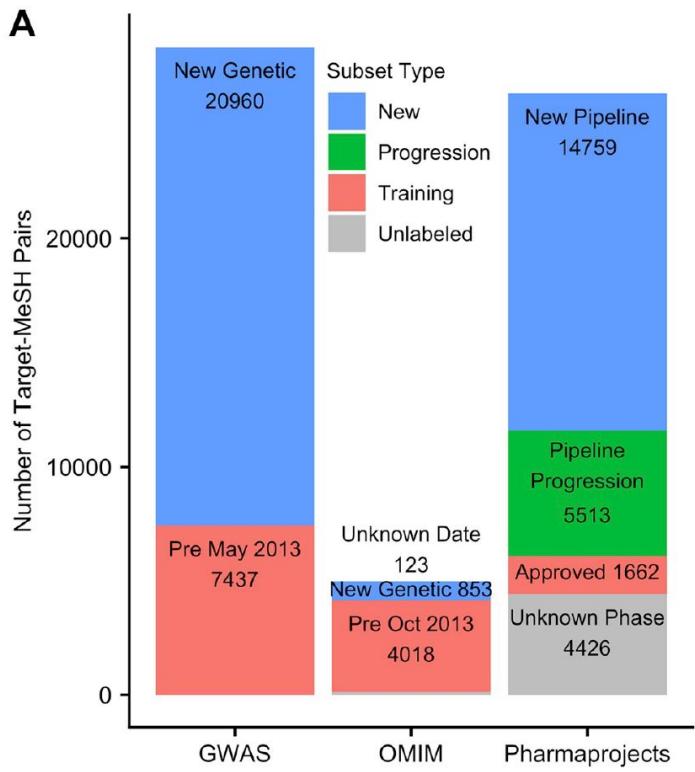
Nelson *et al.* inferred that genetic support offers an likelihood ratio ~2

Table 1 The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

Progression	$p(\text{progress} \text{genetic support}) / (\text{progress} \text{no genetic support})$		
	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

Follow-up study by King et al., 2019



Genes with *biologically understandable* genetic association are more likely to be good targets

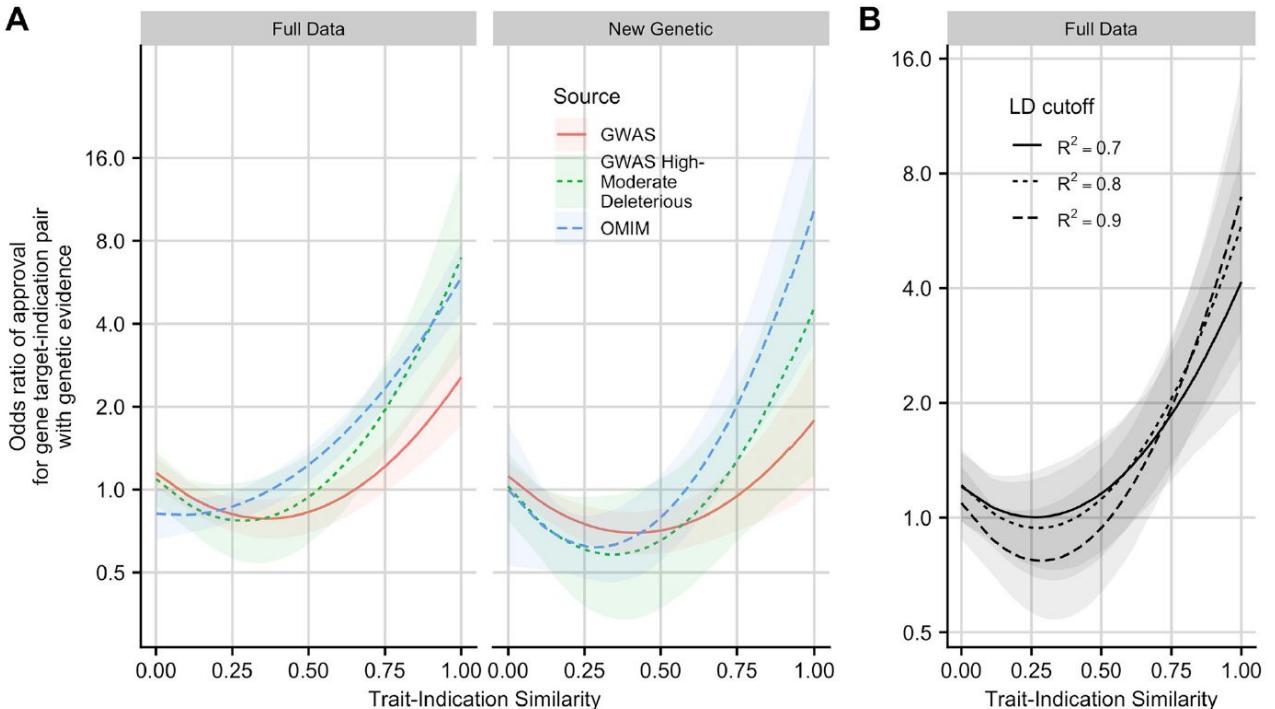


Fig 2. Estimated odds ratio of gene target-indication pair attaining approval, as a function of similarity between drug indication and the most similar trait associated with the target. A: Left: All genetic associations. Right: Only genetic associations reported after 2013 download. B: Effect of LD expansion threshold R^2 on the estimated approval odds ratio of a drug gene target-indication pair supported by a GWAS high-moderate deleterious variant. Posterior median and pointwise 95% credible interval from Bayesian logistic regression.

Discussion

What other evidences can we use to increase the likelihood that a gene is a good drug target?

GOT-IT recommendations for target-disease linkage

Assessment blocks



AB1: target–disease linkage (human targets)

1. Is the target perturbation a cause or consequence of the human disease process?
2. Is the therapeutic relevance (such as human connection) of models used sufficiently high for decision-making?
3. Is the target expression pattern known (that is, within the anticipated patient population)?
4. Is the target manipulation process clinically relevant?
5. Is the read-out used to detect target-dependent processes disease-relevant?
6. Is the stimulus used to activate or influence target-dependent processes disease-relevant?
7. Are the biological consequences of an observed effect size known?

Public resources for target assessment

AB1: target–disease linkage (human targets)

1. Is the target perturbation a cause or consequence of the human disease process?
2. Is the therapeutic relevance (such as human connection) of models used sufficiently high for decision-making?
3. Is the target expression pattern known (that is, within the anticipated patient population)?
4. Is the target manipulation process clinically relevant?
5. Is the read-out used to detect target-dependent processes disease-relevant?
6. Is the stimulus used to activate or influence target-dependent processes disease-relevant?
7. Are the biological consequences of an observed effect size known?

- [OpenTargets](#)
- [Online Mendelian Inheritance in Man](#) (OMIM)

- Scattered in diverse information sources such as [Wikipedia](#) and literature

- Health: [GTEX](#), [The Human Protein Atlas](#)
- Disease: [Gene Expression Atlas](#), scattered

Public resources for target safety assessment

AB2: target-related safety (human targets)

8. Is the target selective and not genetically linked to other diseases (or phenotypes or organ systems)?
9. Is there prior knowledge on safety of the target or reported evidence for the role of the target in a known pathway and/or physiological process that may be harmful if disrupted?
10. Are in vitro or pharmacologically relevant animal models available for safety testing?
11. Do models used for safety testing translate well to humans?
12. Are safety biomarkers available and can adverse effects be monitored and/or predicted by safety biomarkers?
13. Is there sufficient confidence that a necessary safety window has been or can be established?
14. Is the disease life-threatening (at what stage of the disease is the target of relevance)?
15. Is the tissue distribution of the target known (in humans or in animals)?

- [Comparative Toxicogenomics Database \(CTD\)](#)

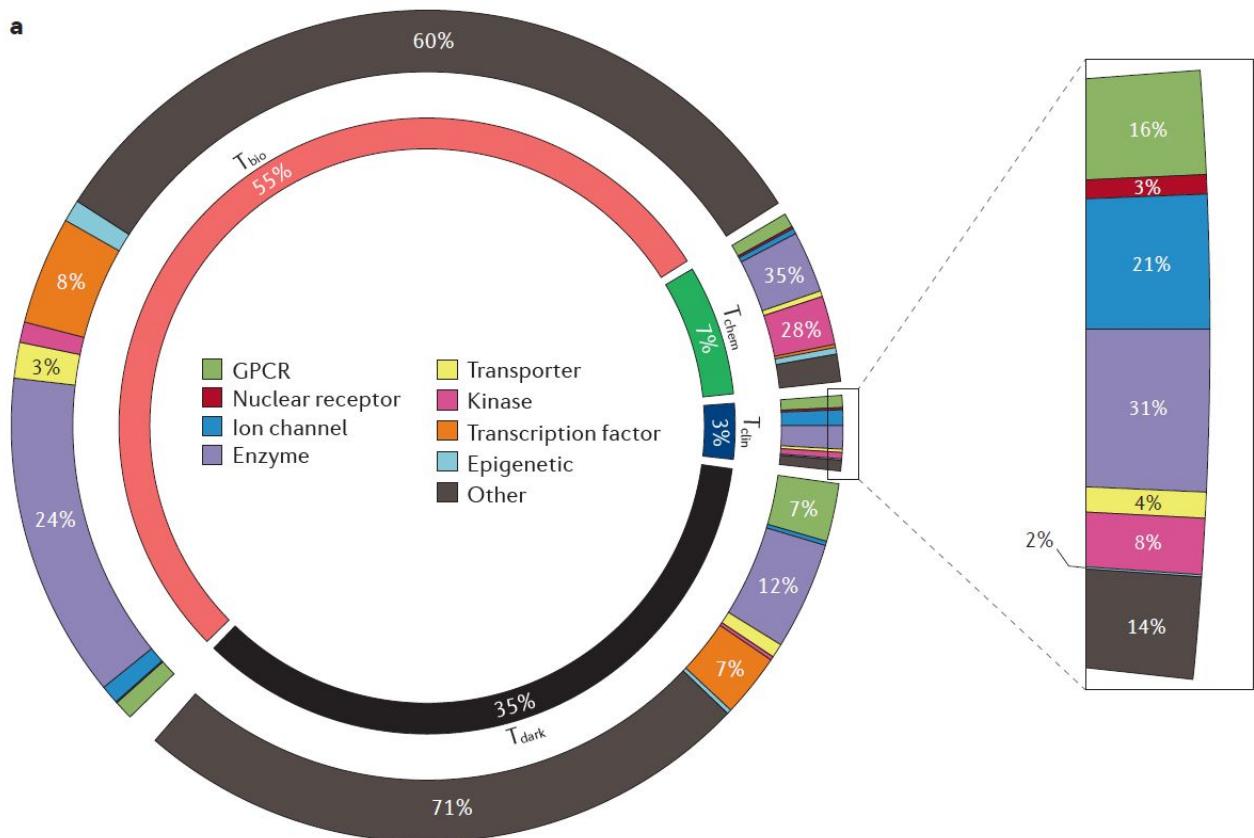
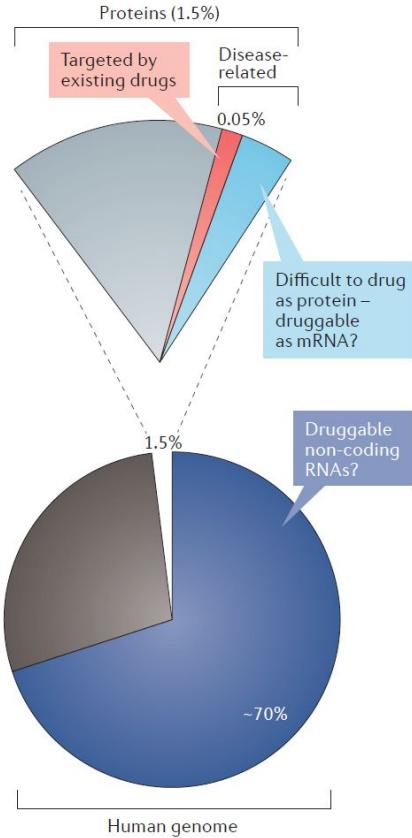
- [DrugBank, DrugCentral](#)
- [FDA Adverse Event Reporting System \(FAERS\)](#)

- [NCBI HomoloGene](#)
- [ENSEMBL ComparaGenom](#)
- [Mouse Genome Informatics \(MGI\)](#)

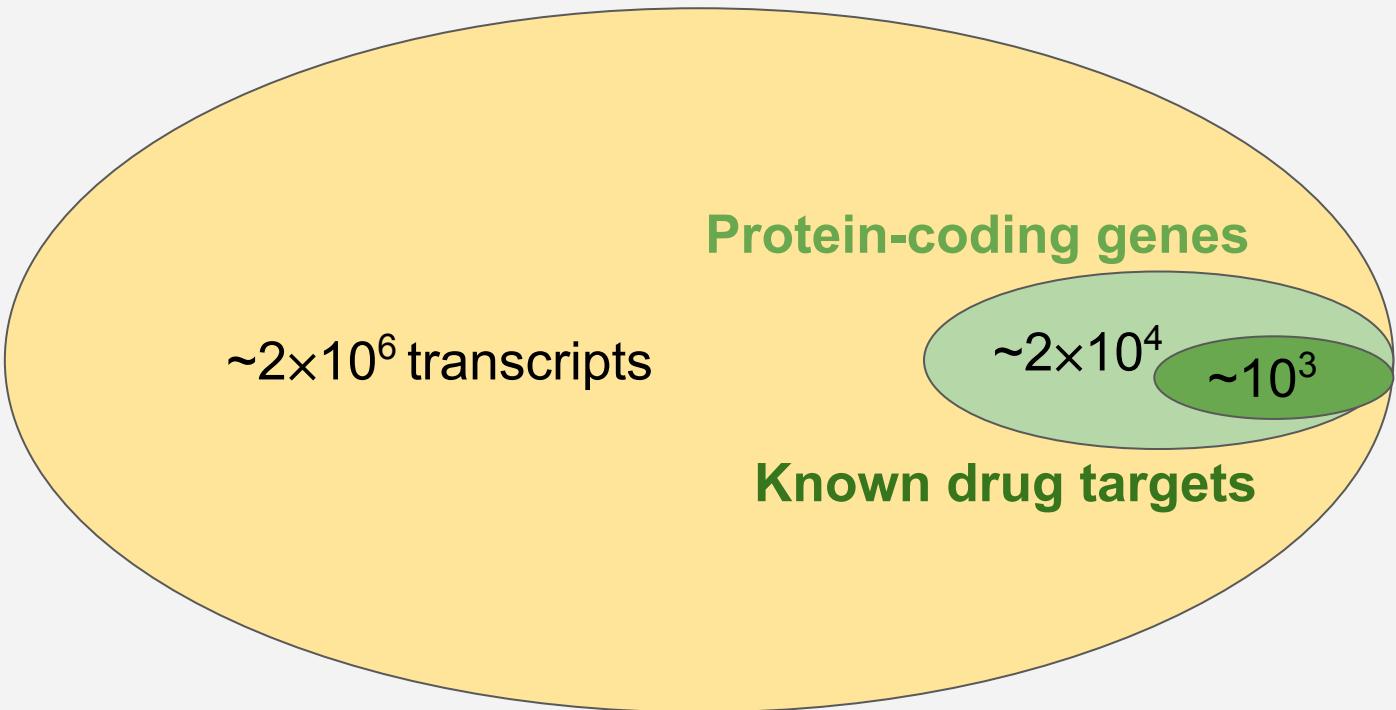
Other important information resources

- **Genomic variations:** [gnomAD](#), [dbSNP](#), and [TCGA](#) for oncology;
- **Protein domain and static structure:** [InterPro](#), [Pfam](#), and [PDB](#);
- **Interaction network and pathway:** [BioGRID](#), [IntAct](#), [Reactome](#), and [KEGG](#);
- **Gene expression profiles associated with the target:** [NCBI GEO](#) (Gene Expression Omnibus), [ARCHS4](#)

Challenge #1: little experience for much of the genome

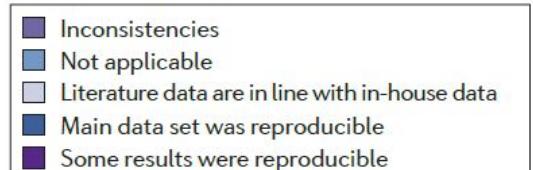
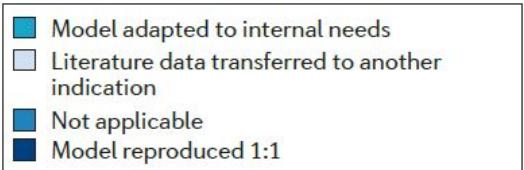
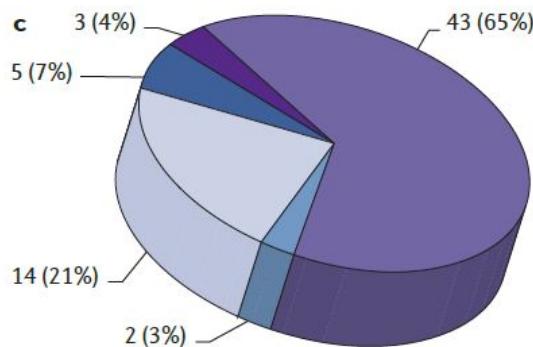
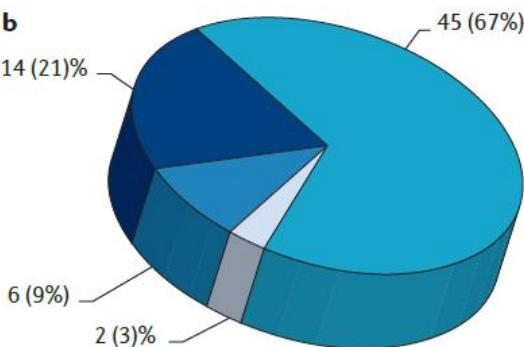
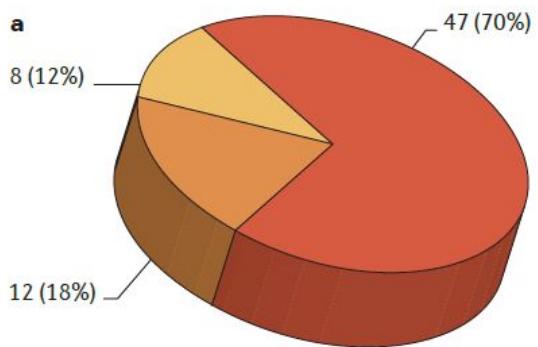


Protein, RNA, or DNA as target?



$\sim 3 \times 10^9$ DNA bases from maternal and paternal each

Challenge #2: Lack of reproducibility

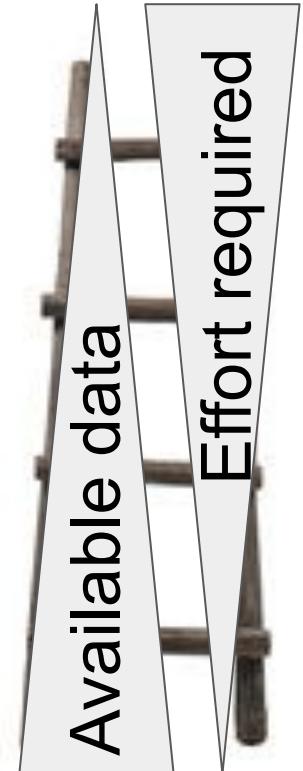


d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Challenge #3: The Target Ladder

3. [Real-world test] What would happen if we inhibit the activity of the kinase domain in the *WKN3* gene in patients with Alzheimer's Disease?
2. [Intervention] What would happen to human cells or to a rat model if we inhibit the activity of the kinase domain in the *WKN3* gene?
1. [Association] What are the evolutionary conservation, sequence, expression profile, expression regulation patterns, ... of the *WKN3* gene?



Conclusions

- Genomics and genetics offer unprecedented opportunities and challenges for target identification and assessment;
- Target identification and assessment involves knowledge integration and experimental validation;
- A central task of mathematical and computational biology in drug discovery is to perform inference, i.e. using information to reduce uncertainty.

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An example of complementary views

We want to work on hepatocarcinoma (liver cancer) and have the following information about a potential target X:

- X is a receptor expressing on the surface of most cell types;
- Upon binding ligands, X activates innate immune response;
- Gene sequence of X is conserved in primates but *not* in rodents;
- Protein X interacts with protein Y, which is essential, namely Y knockout causes lethal embryos;
- Asian population has a unique genetic variant in the non-coding region of X;

Discussion: what are the consequences of having these information?